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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/323,765	06/01/1999	MARK D. SCOTT	259.006US1	9616

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EXAMINER	
HAYES, ROBERT CLINTON	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/323,765	SCOTT ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,28 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment submitted 11/26/04 has been entered.

2. The rejection of claims 14, 19-23 & 31 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn due to the amendment of the claims.

3. The rejection of claims 1, 4, 8, 14-16, 24 & 26 under 35 U.S.C. 102(a) as being anticipated by Jeong et al. (1996) is withdrawn after the PTO library was able to confirm that Jeong et al was not available to the public until Sept. 5, 1996, versus May 1996 as previously made of record by the Examiner. However to clarify the record, Applicants unfortunately never submitted "an official correspondence from Marcel Dekker clearly identifying the publication date of the Jeong at al. article", as asserted in their 1/23/02 response. For the record, the claimed priority date is 6/23/96.

4. Applicant's arguments filed 11/26/04 have been fully considered but they are not deemed to be persuasive.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claim 28 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons made of record in Paper No. 13 (mailed 4/10/01) & 16 (mailed 10/03/01), and as follows.

Claim 28 still recites "the method of claim 21", wherein claim 21 alternatively is directed to a "cellular composition" (i.e., a product, and not a "method" as currently claimed).

It is suggested that amending claim 28 to "the cellular composition [method] of claim 21" should obviate this rejection.

7. Claims 2-7, 18-21, 22-25, 28 & 31 stand rejected under 35 U.S.C. 102(e) as being anticipated by Desai et al. (U.S. Patent 5,578,442), *in light of* Lin et al. *(1976)* for the reasons made of record in Paper No. 13 (mailed 4/10/01), 16 (mailed 10/03/01) & 20040601, and as follows.

In contrast to Applicants' assertions on pages 19-20 & 22-26 of the response, and as previously made of record, Desai clearly teach "covalent bonding" through, for example, free radical polymerization (i.e., col. 4, lines 40-54; col. 5, lines 13-26), **and through** UV-crosslinking (e.g., col. 3, lines 57-61), and as supported by Desai's statement that "[i]*n addition, the* ***further*** *crosslinking of the graft polymer forms a highly stabilized* [i.e., covalent binding], immuno-protective coating of water-soluble [i.e., hydrophilic, by definition] polymer about the treated cell or tissue" [emphasis added], therefore at antigenic sites present in all membrane-bounded proteins, by definition (column 3, lines 53-56). As support that it is well known in the

art that UV-crosslinking constitutes formation of a covalent bond, Lin et al. is referenced in this rejection for the teaching that UV-crosslinking forms **covalent bonds** (e.g., page 947, 1st column). Thus, Applicants' arguments concerning other embodiments taught by Desai (e.g., ionic bonds), or that "it is **impossible** for the polycationic polymers to crosslink with the cells surface" because "three dimensional bonds must be formed..." are not on point, or make little sense in a three dimensional universe. It is noted that Applicants appear to be unaware that MPEP 2123 states that "**patents are relevant as prior art for all they contain**", and that "**nonpreferred embodiments constitute prior art**". In other words, arguments related to other embodiments (even if such are preferred embodiments within the patent) are not on point, especially when these other teachings within Desai et al. are not part of the pending rejection.

Thus, the rejection made of record clearly establishes a *prima facie* case for anticipation because Desai's polycationic species are clearly "hydrophilic ["water-soluble"], biocompatible, [and] non-immunogenicity providing compound or polymer", form "highly stabilized" covalent bonds with membrane-bounded proteins (i.e., antigenic sites, by definition) after free radical-induced or UV-induced crosslinking (which Lin et al teach results in covalent bond formation), and because the instant rejection is consistent with that held by the court in *Ex parte Gray, In re Best, In re Brown, In re Thorpe,* and *In re Marosi* previously made of record.

To further clarify the record, claim 28 is interpreted to be directed to the "cellular composition" of claim 21. It is further noted that no claims are directed to "the virus particle surface" (e.g., pg. 23, lines 21-22 of the response).

In summary, Desai et al. teach non-immunogenic cell compositions, as well as methods to produce these compositions, in which non-ionic water soluble polymers (i.e., hydrophilic/

biocompatible; col. 4, lines 15-31 & 40-54) are covalently attached to viable, nucleated, mammalian cells/tissue through free radical polymerization (i.e., col. 4, lines 40-54; col. 5, lines 13-26; as it relates to claims 2, 6-7, 18 & 24-25), in which substances, such as polysaccharides (e.g., dextran; as it relates to claim 10) or the polyalkylene glycol, PEG (i.e., as it relates to claim 8), are not toxic (i.e., col. 4, lines 15-31; as it relates to claims 3 & 5), and in which attachment to antigenic determinants, as recited, inherently occurs, as does the property that these cells remain viable/survive for over 96 hours (i.e., as it relates to claim 2); absent evidence to the contrary. In that no "by-products"' from the free radical polymerization (i.e., especially as it relates to UV-crosslinking; col. 3, lines 57-61) reasonably exist or remain after washing the treated cells to remove non-reacted hydrophilic polymers, the limitations of claim 4 are met. In that free radical/covalent attachment of polycationic/anionic linkage species are also disclosed (e.g., cols. 4-5 for polycationic species; col. 5-6 for anionic species), the limitations of claims 7 & 24-25 are met. Finally, nucleated cell compositions, and methods of producing such, include islets (i.e., as it relates to claim 22), hepatocytes and neuronal cells (col. 5, lines 27-33; as it relates to claims 20-21 & 31), "secreting cells" (i.e., vascular endothelial cells; as it relates to claims 22 & 19), as well as the epithelial cells contained in Desai's "cells having a modified surface" (i.e., col. 4, line 47; col. 5, lines 27-37; as it relates to claim 23), which are further normally "part of a tissue or organ"' (i.e., as it relates to claim 28), and reasonably alive (i.e., as it relates to claims 2-7 & 24). It is noted that any reaction with cyanuric chloride (i.e., as recited in claims 18, 28 & 31) would not reasonably change the covalent bonds formed, because covalent bonds are covalent bonds, and because the instant claims are not directed to a method, but to a product (i.e., a cellular composition).

Note that Lin et al is referenced in this rejection to establish that it is well known in the art that UV-crosslinking forms **covalent bonds** (e.g., page 947, 1st column).

8. Claims 1, 4, 8, 10-16, 24 & 26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Francis et al. (WO 95/06058), for the reasons made of record in Paper No. 13 (mailed 4/10/01), 16 (mailed 10/03/01) & 20040601, and as follows.

It is noted that Applicants previously acknowledged in their 1/23/02 response that "Francis does apparently incidentally show the covalent bonding of a moiety (including PEG, the erythrocytes of Example 7) to the surface of a red blood cell...", but done for a different purpose, which alternatively and inherently supports the rejection made of record for these claims; consistent with that held by the courts in *Ex parte Gray, In re Best, In re Brown, In re Thorpe* and *In re Marosi* previously made of record. Thus, Applicants' arguments to claim limitations not recited in the claims are moot, and because whatever Francis' intent may have been, or not, is immaterial to whether Francis teach the currently and broadly *claimed* products in this 102 rejection. In other words, inherent properties (i.e., "an anti-immunogenic effect") are inherent whether they are recognized by a reference, or not, and where "motivation" is a consideration under 35 U.S.C. 103, and not 35 U.S.C. 102. It is further noted that any unexpected results related to the degree of anti-immunogenic effect, as assayed within the instant specification (e.g., Example IX) does not obviate a rejection under 35 U.S.C. 102, because structurally Francis cells used other compounds recited in the instant claims to make their non-immunogenic cell products.

Note that **only claim 9** recites use of a methoxy-polyalkylene glycol, which is not part of this rejection, because Francis used TmPEG vs CmPEG (methoxy-polyalkylene glycol), and unexpectedly changed the non-immunogenic component of the product made in the recited product-by-process recitation. It is noted that only TmPEG has been disclosed within the specification to exhibit "no immunological modification" to RBCs (see pg. 30 of the instant specification). Lastly, note that arguments directed to claim limitations in claim 9, which is not rejected over Francis et al., are moot.

In summary, Francis et al. teach non-aggregating, non-immunogenic, anuclear and viable mammalian erythrocyte compositions (i.e., red blood cells) through covalent attachment of the methoxy polyalkylene glycol, TMPEG, as well as methods to produce these compositions (pgs. 64-65, Example 7; as it relates to claims 1, 8, 13-16, 24 & 26), in which polyalkylene glycols are not toxic at the concentrations used (pgs. 14 & 52), as evidenced by no disruption of the cell membrane (i.e. pgs. 64-65), and in which no "by-products" from the covalent attachment of PEG reasonably exist or remain after washing the treated cells to remove non-reacted PEG moieties, etc. (i.e., as it relates to claim 4). However, importantly, Francis also teach that covalent attachment of other polymers, such as dextran and ficoll (pg. 33; as it relates to claims 10-11) and arabinogalactan (pg. 32; as it relates to claim 12) can be used to improve pharmacological properties of target molecules (pgs. 14 & 52).

9. Claims 1-26, 28 & 31 strand rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al., ***in light of*** *Lin et al. (1976),* and **in view of** Francis et al. (WO 95/06058), for the reasons made of record in Paper No. 13, 16 & 20040601, and as follows.

In contrast to Applicants' assertions, the instant rejection does not stand or fall solely on the teachings of Francis et al., especially in light of the further evidence provided by the Examiner concerning the teachings of Lin et al.; which remains consistent with that held by the court in *In re Brown*, previously made of record.

Thus, the teachings of Desai et al., *in light of Lin et al.*, and in view of Francis et al., clearly give rise to non-immunogenic cells by virtue of the intrinsic properties of the cells made by Desai et al., in view of Francis et al., which would be non-immunogenic, by definition. In other words, Applicants' arguments do not accurately address the actual rejection made of record, and therefore, are not persuasive. It is suggested that Applicants re-read the pending rejection.

In summary, Desai et al. is as set forth above for claims 2-7, 18-21, 22-25, 28 & 31. However, Desai do not specifically disclose non-immunogenic cellular compositions comprising anuclear cells/red blood cells, or methods of producing such.

Francis et al. is as set forth above for claims 1, 4, 8, 10-16, 24 & 26. However, Francis et al do not teach covalent attachment of other PEG derivatives, or other polymers, to nuclear cell surfaces.

It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to include Francis' red blood cells (RBCs), and alternate methods of covalently attaching other non-immunological polymers to cells (i.e., including any methoxy-polyalkylene glycols (mPEG) as implicitly suggested by Francis (but except for TmPEG based solely on the unexpected results within the instant specification); as it relates to claim 9), in Desai's non-

immunological cell compositions, because of the common problems of non-compatible antigenic sites between different species/individuals for both nuclear and anuclear cells (i.e., RBCs and platelets), especially if such tissue/blood is scarce, and because Desai et al. disclose in their Detailed Description of the Invention that "[t]he process of the present invention can be used for rendering non-immunogenic *any* cell, tissue, organ, or system of organs, and the like, that may be used for transplant or the like [emphasis added]" (col. 6, lines 15-18; as it relates to claim 28); thereby, providing the motivation for using any cell type, including RBCs , platelets, lymphocytes, and vascular endothelial cells, pancreatic cells and epithelial cells (i.e., as it relates especially to claims 15-16, **17**, 18, 19, 20-21, 22, 23, 26 & 28) as a substrate for making non-immunogenic cell compositions.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for this Group is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
April 14, 2005

ROBERT C. HAYES, PH.D.
PATENT EXAMINER